Esophageal Melanocytosis
Morphologic Features and Review of the Literature
Fuju Chang, MD, PhD; Harriet Deere, MBBS, MRCPath

During early embryogenesis, melanocytes migrate from the neural crest to the epidermis, hair follicles, oral cavity, nasopharynx, uvea, leptomeninges, and inner ear. The esophagus usually lacks normal melanocytes, and the existence of melanocytic lesions, including primary malignant melanoma of the esophagus, was controversial for many years.1 However, aberrant migration of melanocytes during embryogenesis does occur and basal melanocytes have been found in a small number of normal esophagi,2,3 so the occurrence of benign and malignant melanocytic lesions of the esophagus is now well accepted.

Esophageal melanocytosis, also called melanosis, is a rare condition of benign melanocytic proliferation, found in 0.07% to 2.1% of consecutive gastrointestinal endoscopies.4–14 Because of its uncommon nature, many pathologists and gastroenterologists lack experience with this entity. This mini-review summarizes the histopathologic features of esophageal melanocytosis and its differential diagnosis with other pigmented esophageal lesions.

MELANOCYTES OF THE ESOPHAGUS
Melanocytes have their embryologic origin in the neural crest and, during fetal life, migrate to the skin and squamous mucosa through the peripheral nerves. Scattered melanocytes at the interface between the epithelium and the lamina propria of the esophageal mucosa were first described in 1963 by De la Pava et al.2 Of their patients, 4% had esophageal melanocytes. Furthermore, Ohashi et al reported in 1990 that 5 (7.7%) of 65 normal esophageal specimens obtained at autopsy contained melanocytes and microscopic evidence of melanosis.7 All 5 of these specimens contained less than 20 melanocytes per slide section, and in none of the cases was melanosis identifiable grossly.

Like their cutaneous counterparts, basal melanocytes of the esophagus lack desmosomes and tonofilaments but possess long dendritic cytoplasmic processes that extend between the keratinocytes, often passing through several layers of cells.2,3 The nuclei are typically smaller and slightly more hyperchromatic than the nuclei of adjacent keratinocytes. Cells have uniform chromatin and indented nuclear contour. The nucleoli are inconspicuous. Immunohistochemically, these cells are positive for S100, Melan-A, and HMB-45. Electron microscopically, they contain specialized organelles, that is, melanosomes. Melanin pigment is synthesized within the melanosomes and then is inoculated or injected into the cytoplasm of adjacent keratinocytes by the dendritic process of the melanocytes. The melanin pigment is positive with Masson-Fontana staining and negative with Perls iron and periodic acid-Schiff staining. This pigment can be bleached with hydrogen peroxide.

ESOPHAGEAL MELANOCYTOSIS
Clinical Features
Gross or endoscopic esophageal melanocytosis is rare, even less common than microscopic melanosis. This is as expected, because higher concentrations of melanocytes are required before melanocytosis can be observed grossly. To our knowledge, 33 cases of isolated esophageal melanocytosis have been reported in the English literature (Table), together with one extra case recently encountered by us (F.C., oral communication, 2005). Of these, 21 cases were reported in an Indian series7 and 6 cases from Japanese subjects.5,10,11 Interestingly, esophageal melanocytosis appears to be extremely rare in Western countries, with only 5 documented cases (including our own unpublished case) available at the present moment.8,9,12 Our patient was an 80-year-old English woman who presented with bluish black macules in her distal esophagus. Examination of her esophageal biopsies disclosed typical histologic fea-

• Endoscopic or macroscopic esophageal melanocytosis is a benign clinicopathologic entity characterized by melanocytic proliferation in esophageal squamous epithelium and melanin deposition in the mucosa. Little is known about the etiology and natural course of this condition, although it has been suggested to be a precursor of primary esophageal melanoma by some authors. Following a search of the bibliographic databases (PubMed and Medline) regarding esophageal melanocytosis and melanosis, thirty-four cases of isolated esophageal melanocytosis (including one unpublished case from us) were found. The histopathologic features of esophageal melanocytosis are reviewed and its differential diagnosis with other pigmented esophageal lesions is discussed.

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tures of esophageal melanocytosis (see Figures 1 through 3). In the study from India, 21 pigmented melanocyte-containing patches were found in 1000 consecutive routine esophagogastroduodenoscopies, giving an incidence of 2.1%. Overall, esophageal melanocytosis is more commonly seen in men (22 men vs 12 women) and mainly in the middle and lower third of the esophagus (Table).

Endoscopically, esophageal melanocytosis has been described as flat, oval, irregularly delineated lesions. Magnifying endoscopy discloses that the pigmented area consists of granulilike spots and linearly arranged granules. Dumas et al found that 0.07% to 0.15% of patients undergoing upper endoscopy had gross gray or brown esophageal melanosis.4

### Pathologic Findings

Histologically, esophageal melanocytosis is characterized by the presence of increased numbers of melanocytes in the basal layer of esophageal squamous epithelium and an increased quantity of melanin in esophageal mucosa.4,14 On hematoxylin-eosin staining the melanocytes are pigment-laden dendritic cells (Figure 1, A). These cells are positive for melanocytic markers, such as S100 (Figure 1, A), Melan-A, and HMB-45. The underlying lamina propria contains variable pigment-laden macrophages (Figure 2, B). The pigment is coarse brownish black on hematoxylin-eosin–stained slides. It stains positive with the Masson-Fontana method (Figure 2, B), can be bleached completely with hydrogen peroxide, and is negative with both the periodic acid–Schiff and Perls methods. The pigment-laden cells are positive for CD68 (Figure A, A), but negative for melanocytic markers (Figure 3, B).

In most cases, the melanocytes do not exhibit any sign of nuclear or cellular atypia. However, Walter et al described a case of esophageal melanocytosis concomitantly presented with multifocal squamous cell carcinoma in situ. The histologic appearance of this melanocytosis is unusual because of its cytologic atypia in the melanocytic cell population, resembling features of a melanoma in situ. However, the melanocytic lesion disappeared during follow-up, suggesting a nonneoplastic nature.14

The overlying squamous epithelium may exhibit reactive basal hyperplasia, acanthosis, and hyperkeratosis but demonstrates mature differentiation. Moreover, inflammatory cell infiltrate, fibrosis, and areas of telangiectasia are commonly seen in the subepithelial lamina propria.

### Terminology Consideration

Although the term melanosis was used in most of the previous reports, this term does not accurately describe the increased number of melanocytes found in this condition. In addition, this term is a generic term describing conditions in which there is an abnormal grayish black or brownish black pigmentation and does not imply that the underlying pigment is specifically melanin. For example, the melanosis described in the duodenum, ileum, and colon is characterized by the presence of pigmented macrophages containing “pseudomelanin” in the lamina pro-
Figure 1. Esophageal melanocytosis. Biopsy showing increased numbers of pigment-laden dendritic melanocytes and deposition of melanin pigment in the basal layer of the squamous epithelium (A) (hematoxylin-eosin stain, original magnification ×400). Intraepithelial melanocytes are positive for S100 (B) (immunohistochemistry, original magnification ×200).

Figure 2. Esophageal melanocytosis. Numerous pigment-laden macrophages are present in the subepithelial lamina propria (A) (hematoxylin-eosin stain, original magnification ×200). The pigment stains positive with the Masson-Fontana staining (B) (original magnification ×200).

Clinicopathologic Correlation and Differential Diagnosis

Clinicopathologic Correlation

Little is known about the etiological factors and pathogenesis of esophageal melanocytosis. It has been shown that esophageal melanocytosis is mostly located in the middle and lower third of the esophagus and is frequently associated with chronic esophagitis and reactive epithelial changes, such as acanthosis and basal cell hyperplasia. Therefore, the unhelpful term esophageal melanosis should be avoided in pathology reports.
An increase in the number of melanocytes is well recognized to occur in skin in response to noxious stimuli, and it appears that this pattern of response also applies to the esophagus. Because bile fluid and gastric acid are harmful stimuli in the esophagus, it is hypothesized that esophageal melanocytosis may be a result of gastroesophageal reflux disease.\textsuperscript{5,7,8}

Esophageal melanocytosis has also been associated with a variety of systemic disorders, such as Laugier-Hunziker syndrome\textsuperscript{11} and Addison disease.\textsuperscript{12} Endoscopic melanocytosis of the esophagus has been reported in patients with anal melanoma\textsuperscript{13} and esophageal squamous cell carcinoma in situ.\textsuperscript{14} Notably, melanocytosis has been described in 25\% to 30\% of surgical specimens of esophagus containing primary malignant melanomas,\textsuperscript{16-19} and this lesion has been suggested to be a precursor of melanoma by some authors.\textsuperscript{15,17} However, no follow-up information is currently available, and there is no documented case in the literature in which esophageal melanocytosis progressed to esophageal melanoma.

Because gross esophageal melanocytosis is rare, there are not enough data to establish guidelines regarding management, including a requirement for surveillance. There is no report of esophageal melanocytosis that resulted in specific symptoms and special treatments.

**Differential Diagnosis**

Esophageal melanocytosis must be differentiated from benign nevi and malignant melanoma, because melanin deposition is often the main feature in these lesions. Melanocytic nevi are uncommonly seen in the esophageal mucosa. To our knowledge, only a single case of blue nevus is found in the literature, and this was reported by Lam et al\textsuperscript{20} from a 52-year-old Chinese woman who presented with linear patches of bluish pigmentation in her lower esophagus. Like its cutaneous and mucosal counterparts,\textsuperscript{21-26} this is characterized by the presence of dendritic melanocytes in the subepithelial connective tissue without junctional melanocytic activity. The absence of cytologic atypia and the presence of heavily pigmented dendritic melanocytes in stromal tissue differentiate the lesion from melanoma and melanocytosis.\textsuperscript{20}

Primary malignant melanoma of the esophagus is also rare, with an incidence of 0.0036 in 100 000.\textsuperscript{16-19} It represents approximately 0.1\% to 0.2\% of all esophageal neoplasms. So far, less than 200 cases of esophageal melanoma have been published worldwide.\textsuperscript{16-19} Endoscopically, it often presents as pigmented or nonpigmented polypoid mass in the middle or lower esophagus. Histologically, melanoma is composed of epithelioid cells arranged in nests or spindle cells arranged in fascicles, with or without deposition of melanin pigment (Figure 4). The nuclei of the melanocytes were typically large and round or oval with a vesicular chromatin pattern and distinct or prominent nucleoli. Nuclear pseudo-inclusions were often readily identified. Most of the tumors are highly cellular and contain numerous mitotic figures. If a tumor is amelanotic, it may be difficult to recognize as malignant melanoma without ancillary immunohistochemical staining. Lentiginous or pagetoid intraepithelial spread is often present in esophageal mucosa adjacent to the invasive melanoma (Figure 5). These intraepithelial melanocytes are apparently atypical and frankly malignant in nature and are readily distinguishable from the simple melanocytosis.

In addition, clinical and endoscopic differential diagnoses of esophageal melanocytosis should theoretically include anthracosis, exogenous dye ingestion, hemosiderosis, and lipofuscin deposition (pseudomelanosis).\textsuperscript{15,27-30} These lesions could be easily excluded after histologic and histochemical examination.\textsuperscript{27} A dark-pigmented esophageal mucosa, the so-called black esophagus, is a rare observation during upper endoscopy.\textsuperscript{20} It appears endoscopically as a dark-pigmented esophagus with ulcerations which corresponds to severe acute inflammation with mu-
cosal necrosis seen on histologic examination. The etiological factor involved seems to be ischemic injury caused by arteriolosclerosis, arterial thrombosis, or aortic dissection. Blue rubber bleb nevus syndrome is also a rare condition characterized by the presence of multiple bluish, slightly raised angiomatous lesions of the skin and the gastrointestinal tract, causing anemia through chronic bleeding. Histologically, these lesions are characterized by a variety of vascular alterations, ranging from capillary telangiectasias to cavernous hemangiomata with arteriovenous communication, the latter being the most common finding. In both black esophagus and blue rubber bleb nevus, hemosiderin pigment and siderophages may be present, but melanocytes and melanin pigment are not seen.

**CONCLUSION**

Esophageal melanocytosis is a benign condition defined as melanocytic proliferation in the basal layer of esophageal squamous epithelium and an increased quantity of melanin in esophageal mucosa. This is a rare but well characterized clinicopathologic entity. The term esophageal melanosis should be avoided because it does not accurately describe the increased number of melanocytes or specify the melanin nature of the pigment found in this condition. The etiology and pathogenesis remain uncertain, although it has been hypothesized that esophageal melanocytosis may be a result of gastroesophageal reflux disease and other chronic stimuli which cause mucosal damage and keratinocytic hyperplasia. Differential diagnoses of esophageal melanocytosis from its histologic mimics include benign melanocytic nevi and malignant melanoma. The possible association of melanocytosis with primary esophageal melanoma is intriguing and awaits further investigations. At this time, there are not enough data to discern whether the association implies related pathogenesis or simply reflects the occurrence of 2 entities in the same patient. More widespread recognition by gastroenterologists and histopathologists would be worthwhile for a better understanding of esophageal melanocytic lesions.

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**References**


*Esophageal Melanocytosis—Chang & Deere*